

Review Article

Supat Chamnanchanunt*, Ponlapat Rojnuckarin

Direct oral anticoagulants and travel-related venous thromboembolism

<https://doi.org/10.1515/med-2018-0085>

received October 21, 2017; accepted October 26, 2018

Abstract: Travel-related thromboembolism reflects the relationship between venous thromboembolism (VTE) and long-haul flights. Although this condition is rare, it may cause significant morbidity and mortality. Therefore, travelers should be evaluated for the risks for thrombosis. Travel physicians should employ a clinical risk score and select investigations, prophylaxis, and treatment that are appropriate for each individual. This review summarizes current VTE clinical risk scores and patient management from various reliable guidelines. We summarized 16 reliable publications for reviewing data. Direct oral anticoagulants (DOACs) are currently the standard treatment for VTE and a prophylactic measure for VTE in orthopedic surgery. Compared with a vitamin K antagonist (VKA), DOACs show better safety and similar efficacy without the need for monitoring, and have fewer food/drug interactions. Inferred from the data on general VTE, DOACs may be used to treat travel-related VTE. Although the data are lacking, DOACs may be used off-label as VTE prophylaxis. Before using DOACs, physicians must know the pharmacology of the drugs well and should realize that the availability of antidotes for bleeding complications is limited.

Keywords: Apixaban; Dabigatran; Edoxaban; rivaroxaban; Venous thromboembolism; Aviation medicine; Travel-related illness

*Corresponding author: **Supat Chamnanchanunt**, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, 10400, (+66)2-6435-598, E-mail; Supat.cha@mahidol.edu

Ponlapat Rojnuckarin, Division of Hematology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, 10330, (+66)2-2256-4000 Ext 80252, E-mail; rojnuckarin@gmail.com

1 Introduction

Travelers' thrombosis was first reported in 1954 demonstrating the relationship between long haul flights and venous thromboembolism (VTE: Deep vein thrombosis [DVT] and/or pulmonary embolism [PE]). This condition has also been referred as "travelers' syndrome" which the World Health Organization (WHO) agreed that there was an associated clinical risk of occurring with venous thrombosis after long hauls [1,2]. The incidence rates were based on a small number of cases and they usually occurred with the presence of other VTE risk factors in most of the patients [3].

The term 'economy class syndrome' was postulated at the beginning because the first four patients reported with VTE in 1954 were economy class passengers [4]. Those patients were lying in a recumbent posture, and therefore this is a seriously misleading term. From the BEST study, there was no difference between the incidences of VTE between business and economy seat classes in the same flight [1].

2 Travel-related venous thrombosis

Twelve prospective studies on travel-related VTE showed incidence rates ranging from 0 – 25% [1,2,5-14]. The variable rates are attributed to variations in research methodology, study populations, outcome measurements (symptomatic or asymptomatic VTE) and risk factors. Four studies concentrated on low-risk travelers [1,8,13,14], while the rests included high-risk travelers in their studies [9-11]. The study by Scurr and colleagues showed that 10% of patients presented with asymptomatic VTE [8].

According to Rudolf Virchow, VTE is caused by a classical triad composed of immobility, vascular endothelial damages, and blood hypercoagulability. The mechanism of travel-related thrombosis was postulated to be from blood stasis at the extremities of sitting in a small space while traveling more than 8 hours [3,14]. Dehydration may result in hemoconcentration of clotting factors. In

addition, reduction of oxygen in the cabin room caused over-activation of the coagulation cascade [15-18].

The recommendations for traveler's thrombosis were included in 4 guidelines [German, British, International Consensus and American College of Chest Physicians guidelines] [19-22]. American College of Chest Physician (ACCP) suggested a score for the risk assessment of travel-related VTE comprising advanced age, previous history of VTE, active malignancy, previous surgery or trauma within a few weeks, pregnancy, estrogen use, immobility, and known history of thrombophilic disorders. If travelers have one of the risk factors, they were classified in an increased risk group [23]. However, German, British and International consensus guidelines did not suggest a score for risk stratification of travelers [19,20,22].

Regarding the prophylaxis, non-pharmacological methods were recommended for preventing blood stasis among low-risk groups. The preventive measures include attempting to stand or move around every 2 hours for a few minutes and engaging in flexion-extension exercise while seated. In addition, travelers should avoid dehydration, excessive alcoholic or caffeine intake and do not use tight clothing to decrease the risk of VTE during long haul flights [24].

Concerning pharmacological or interventional methods for preventing VTE, all four guidelines suggested two interventions (compressive stocking and anticoagulants) for intermediate and high-risk groups to prevent travel-related VTE. Compressive stocking below knee was recommended for travelers with at least one of risk factors as followed; advanced age (above 60 year-old), previous history of VTE, active malignancy in the last 6 months (or patients with awaiting surgery or chemo-radiotherapy or in palliative phase), chronic venous insufficiency, severe obesity (body mass index $> 30 \text{ kg/m}^2$), postpartum within 6 weeks, previous history of unprovoked VTE or travel-related thrombosis, previous surgery within 4 weeks, pregnancy, estrogen use or known thrombophilic disorders. On the other hand, the international consensus guideline also recommended compression stocking in subjects with 2 or more risk factors [22]. Two randomized control trials showed a significant reduction in leg edema without any adverse events among compression stockings group [25,26]. Moreover, superficial vein thrombosis was reduced among travelers who used compression stockings. Compression stockings can help blood return from superficial veins and back to the heart.

Both British and International consensus guidelines suggested anticoagulant prophylaxis among very high-risk groups (previous history of VTE, previous history of unprovoked VTE or travel-related thrombosis, post major

surgery within 4 weeks, active malignancy within the surgery/chemo-radiotherapy/palliative phase) [20,22]. The rest of the patients showed no sufficient data of clinical benefit from anticoagulants.

Thrombosis after flights can occur among travelers with underlying diseases (for example active malignancy). Heparin and low molecular weight heparin (LMWH) have been approved for VTE prophylaxis in both medical and surgical conditions and, therefore, may be used in these patients. However, the need for injections makes them impractical. Vitamin K antagonists (VKA) are also not appropriate as they require at least 4-5 days to achieve full actions. Direct oral anticoagulants (DOACs) are rapid-acting by 2 hours after ingestion and do not need injection. Therefore, DOACs are very good candidates for VTE prophylaxis before travel. However, there has been no evidence-based recommendation in this setting. Furthermore, DOACs are only approved for the treatment of VTE and prophylaxis of VTE after major orthopedic surgery.

3 Anticoagulant treatment of thrombosis after the flight (TAF)

The aims of treatment of thrombosis are to stop venous clot progressions and prevent further clot in the future. The goals usually are achieved with anticoagulation using low-molecular-weight heparin (LMWH) followed by vitamin K antagonist (VKA; warfarin) [27]. The LMWH can be injected once or twice daily as it has a longer biologic half-life, dosing is adjusted per patient body weight, and blood testing is not required. Heparin-induced thrombocytopenia appears to be less likely compared with standard heparin. The time to withdraw from LMWH injection (short-term anticoagulation) is when patients have reached a therapeutic level of warfarin [28].

The duration of warfarin treatment depends on whether the patients have a first episode of venous thrombosis and reversible risk factors (for example a long haul flight) for thrombosis. Recommendation for treatment is at least 3-6 months [20]. Three months are sufficient if the reversible factors removed, but recurrent VTE requires long-term anticoagulation. Symptomatic isolated calf-vein thrombosis requires 6 – 12 weeks of treatment [29]. Physicians should be aware that both recurrent VTE and bleeding complications are increased in cancer patients [23]. With the discovery that long haul flight is associated with venous thrombosis, the question of the benefits of DOACs in this setting has been raised.

4 Methods

4.1 Search Strategy Methods and Study Selection

We analyzed the medical journals for published studies on oral anticoagulants for thrombosis treatment. The MEDLINE database, Google Scholar, PubMed searches were used and limited to journals using the English-language. The Medical Subject Headings (MeSH) or keywords phrases were “apixaban”, “dabigatran”, “edoxaban”, “rivaroxaban”, “venous thromboembolism”, “deep vein thrombosis”, “pulmonary embolism”, “aviation medicine” and “travel-related illness”. We reviewed the reference lists of additional journals not captured in our initial search. We had 4,889 publications after use those keywords, and then we excluded 4,504 publications without full download or no English version. We also excluded 369 publications without a randomized clinical trial. Finally, we enrolled 16 publications for reviewing data according to our scope of interest.

5 Results

5.1 Role of new oral anticoagulants

In general practice, the treatment of venous thromboembolism (VTE) as suggested by evidence-based guidelines was to use subcutaneous low-molecular-weight hepa-

rins (LMWHs) followed by vitamin K antagonists (VKAs; warfarin can be used with dose adjustments according to international normalized ratio (INR) at the target range of 2.0 to 3.0). LMWH is inconvenient for the patients because it needs subcutaneous injections. Moreover, drug-drug or drug-food interactions may frequently occur with VKA usage, and INR needs to be frequently monitored. Therefore, new DOACs were developed to overcome those disadvantages and to increase compliance of the patients.

5.2 Direct oral anticoagulants

Direct oral anticoagulants (DOACs) are orally administered and do not need coagulation blood testing. The mechanism of action of new oral anticoagulants is either a direct thrombin inhibitor (dabigatran) or specific factor Xa inhibitor (apixaban, edoxaban, or rivaroxaban). They have short times to peak concentrations, ranging from 1.0 – 4.0 hours, except for apixaban which has a delayed time to peak concentration.

Thrombin inhibitor and its pharmacological characteristics (Table 1)

5.3 Dabigatran etexilate

Dabigatran (prodrug's name; dabigatran etexilate; Pradaxa®; product of Germany) is a thrombin inhibitor with only 6% bioavailability and 80% renal clearance. A half-life of dabigatran is 12.0 to 17.0 hours, and its absorption is prevented by P-glycoprotein (P-gp) [30].

Table 1: Pharmacological characteristics of the vitamin K antagonist and the direct oral anticoagulants [2,24,30]

Characteristics	VKA	Thrombin inhibitor	FXa inhibitor		
Name	Warfarin	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Prodrug	Drug	Prodrug (dabigatran etexilate)	Drug	Drug	Drug
Bioavailability (%)	60-95	6	50	62	>80
Time to peak concentration (hours)	1.0 – 4.0	1.5 – 2.0	3.0 – 4.0	1.0 – 2.0	2.0 – 4.0
Half-life (hours)	35 – 45	12 – 17	8 -15	9 -10	5 -9
Renal clearance (%)	<10	80	25	35- 49	33
Hepatic clearance	+	+	+	+	+
Metabolism	CYP450	P-gp	P-gp, CYP3A4	P-gp, (CYP3A4)	P-gp, CYP3A4
Precaution	Food and drug affect	Absorption delayed, not reduced	No	No	Required for absorption of dose > 10 mg

P-gp; P-glycoprotein or permeability glycoprotein, CYP450; cytochrome P450, CYP3A4; cytochrome P3A4

5.4 Treatment with dabigatran

A phase III trials for the treatment of VTE (dabigatran *versus* VKA in RE-COVER-I, RE-COVER-II and RE-MEDY trials and dabigatran *versus* placebo in the extension phase of RE-SONATE trial) showed that the efficacy of dabigatran 150 mg twice daily was non-inferior in the venous thrombosis treatment with a significantly lower non-major bleeding compared to the standard regimen [31-33]. A combined result of RE-COVER-I and RE-COVER-II studies with extended follow-up periods (224 days) showed to be non-inferior compared to the standard regimen (both VTE related complications and safety aspects) [31,33]. For treatments after 3-6 months, the RE-MEDY study showed non-inferior benefits between dabigatran and VKA at 36 months (VTE recurrence 1.8% *versus* 1.3%) [32]. The RE-SONATE study conducted in 1,343 patients showed a significantly lower risk of VTE related complications (0.4% *versus* 5.6%) compared to placebo [32].

Factor Xa inhibitors and its pharmacological characteristics (Table 2).

5.5 Apixaban

Apixaban (Eliquis®; product of USA) is a direct FXa antagonist that has 50% bioavailability and 25% renal clearance. A half-life of apixaban is 8.0 to 15.0 hours, and its absorption is prevented by P-gp. It is metabolized through CYP3A4 [30].

5.6 Treatment of apixaban

In the randomized dose-ranging Botticelli study, patients were grouped into 3 dosages of apixaban (5 mg twice daily, 10 mg twice daily or 20 mg once daily) and showed similar VTE related complications and safety rates among three apixaban doses. The results of any doses of apixaban were similar to the standard regimen (LMWH followed by VKA) in the incidences of VTE related complications (4.7% *versus* 4.2%) and major bleeding rates (7.3% *versus* 7.9%) [34]. The randomized AMPLIFY trial enrolled 5,395 symptomatic VTE patients to demonstrate a significantly lower risk of VTE related complications compared to standard regimen at 1 month of follow-up. The major bleeding rate of apixaban in AMPLIFY study was low when compared to the standard regimen [35]. Interestingly, in the AMPLIFY-EXT study, a low apixaban dose (5 mg/day) showed a significantly lower risk of VTE related and bleeding com-

plications compared to regular apixaban dose (10 mg/day) and placebo ($p < 0.001$) at 1 year of follow-up [36].

5.7 Edoxaban

Edoxaban (Lixiana-Savaysa®; product of Japan) is a direct FXa antagonist that has 62% bioavailability and range from 35 to 49% of renal clearance. A half-life of edoxaban is 9.0 to 10.0 hours, and its absorption is inhibited by P-gp as an efflux pump and uses cytochrome 3A4 (CYP-3A4) for metabolism [30].

5.8 Treatment with edoxaban

There was one study (the Hokusai-VTE) conducted in 8,240 acute symptomatic DVT or PE patients, the patients with edoxaban (both 60 mg or 30 mg once daily) was found to be non-inferior in the venous thrombosis related complications and had a significantly lower risk of major bleeding compared to standard regimen (VKA) [37].

5.9 Rivaroxaban

Rivaroxaban (Xarelto®; product of Germany) also is a direct FXa antagonist with more than 80% bioavailability and 33% renal clearance. The half-life of rivaroxaban is 5.0 to 9.0 hours and its absorption also uses P-gp as an efflux pump and CYP3A4 is a metabolizer [30].

5.10 Treatment with rivaroxaban

There were seven studies compared between oral rivaroxaban and standard regimen among patients with VTE (the EINSTEIN-DVT, EINSTEIN-EXTENSION, EINSTEIN-PE, Wang et al., post-marketing study (XALIA), J-EINSTEIN-DVT&PE and EINSTEIN-CHOICE). The EINSTEIN-DVT, EINSTEIN-EXTENSION and EINSTEIN-PE studies showed that any dosages of rivaroxaban were found to be significantly non-inferior in VTE related complications and lower incidence of non major bleeding when compared to standard regimens [38-40]. For long-term therapy, rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) was non-inferior to the standard regimen (enoxaparin followed by a VKA) at 1 year follow-up, without differences in bleeding events [38-40]. A J-EINSTEIN-DVT&PE study showed that rivaroxaban 15

Table 2: Clinical data on the use of direct oral anticoagulants in the treatment of venous thrombosis

Author, year (study) [ref.]	Population, n, age, inclusion of conditions (n)	Study drug	Standard regimen (n)	Clinical outcome VT complications (%)	Safety (%)
Dabigatran (DAB)					
Schulmna, 2009 (RE-COVER I)[31]	2,539, age>18 yr, acute proximal DVT or PE	DAB (1,273) oral	VKA (1,266) oral, INR 2-3	2.4 vs 2.1 (p< 0.001) 2.7 vs 2.5 (NS)	MB; 1.6 vs 1.9 (NS) NMB; 5.6 vs 8.8 (p= 0.002)
Schulmna, 2013 (RE-MEDY)[32]	2,856, age >18 yr, acute proximal DVT or PE	DAB (1,430) oral	VKA (1,426) oral, INR 2-3	1.8 vs 1.3 (p= 0.01)	MB; 0.9 vs 1.8 (p= 0.06) NMB; 5.6 vs 8.8 (p= 0.002)
Schulmna, 2013 (RE-SONATE)[32]	1,343, age >18 yr, acute proximal DVT or PE	DAB (681) oral	placebo (662) oral, UNK dose	0.4 vs 5.6 (p< 0.001)	MB; 0.3 vs 0 (p= 1.0) NMB; 5.3 vs 1.8 (p= 0.001)
Schulmna, 2014 (RE-COVER II)[33]	2,568, age >18 yr, acute proximal DVT or PE	DAB (1,279) oral	VKA (1,289) oral, INR 2-3	2.3 vs 2.2 (p< 0.001) 2.7 vs 2.3	MB; 1.2 vs 1.7 (NS) NMB; 5.0 vs 7.9 (NS)
Apixaban (APX)					
Botticelli study, 2008 [34]	520, N/A, symptomatic proximal DVT or extensive calf vein	Dose1; APX (130) Dose2; APX (134) Dose3; APX (128)	LMWH (TIN or ENX or FON 1.0 mg/kg x 7 d), switch to VKA oral,	6.0(dose1)/5.6(-dose2)/ 2.6(dose3) vs 4.2	MB;8.6(dose1)/4.5(-dose2)/ 8.9(dose3) vs 7.9
Agnelli, 2013 (AMPLIFY trial)[35]	5,395, age>18 yr, symptomatic DVT/ PE	APX (2,691)	ENX (2704), S.C. switch to VKA oral	1.5 vs 1.9 (p<0.001)	MB; 4.3 vs 9.7 (p<0.001) NMB; 3.8 vs 8.0 (p<0.001)
Agnelli, 2013 (AMPLIFY-EXT)[36]	2,482, age> 18 yr, symptomatic DVT or PE	Dose1; APX (840) Dose2; APX (813)	Placebo oral (829) UNK dose	1.7(dose1)/1.7(dose2) vs 8.8 (p<0.001)	MB; 0.2(dose1)/0.1(-dose2) vs 0.5 NMB; 3.0(dose1)/4.2(-dose2) vs 2.3 (NS)
Edoxaban (EDX)					
The Hokusai-VTE, 2013[37]	8,240, age>18 yr, acute DVT or PE	Dose1; EDX (4,118) Dose2; EDX,	VKA (4,122),	3.2 vs 3.5 (p< 0.001)	MB; 8.5 vs 10.3 (p= 0.004)
Rivaroxaban (RVX)					
The EINSTEIN, 2010 [38]	3,449, age> 18 yr, acute DVT (EINSTEIN-DVT study)	RVX (1,731)	ENX (1,718), S.C. 1MKD (> 5d) VKA, oral	2.1 vs 3.0 (p<0.001)	MB; 0.8 vs 1.2 (p= 0.21)
The EINSTEIN, 2010 [38]	1,197, age> 18 yr, acute DVT (EINSTEIN-Extension study)	RVX (602),	Placebo (594), oral UNK mg	1.3 vs 7.1 (p<0.001)	MB; 0.7 vs 0 (NS)
Ageno, 2012 (EINSTEIN-PE)[40]	3,449, age>18 yr, acute DVT	RVX (1,731)	ENX (1,718)	2.1 vs 3.0 (p<0.001)	All bleeding; 2.2 vs 2.9 (p= 0.06) MB; 0.8 vs 1.2 (p= 0.21)
Wang, 2013[45]	439, age>18 yr, acute symptomatic DVT or PE	RVX (220)	ENX (219) S.C. 1 MKD (> 5 d), VKA	3.2 vs 3.2 (p= 0.94)	MB; 0 vs 2.3 NMB; 5.9 vs 9.2 (p= 0.19)
Ageno, 2014 (XALIA)[40]	3,449, age > 18 yr, acute DVT with post-marketing study	RVX (1,731)	LMWH or FON (1,718), S.C. 1 MKD (> 5 d), VKA	2.1 vs 3.0 (p< 0.001)	MB; 0.8 vs 2.1 (p= 0.21) NMB; 7.3 vs 7.0

Table 2 continued: Clinical data on the use of direct oral anticoagulants in the treatment of venous thrombosis

Author, year (study) [ref.]	Population, n, age, inclusion of conditions	Study drug (n)	Standard regimen (n)	Clinical outcome	
				VT complications (%)	Safety (%)
Yamada, 2015 (J-EINSTEIN DVT&PE) [41]	97, age > 20 yr, acute DVT or PE	Dose1; RVX (23) Dose2; RVX (55)	UFH/VKA INR 2 (19)	0(dose1)/2.0(dose2) vs 5.3	MB;0.7 (dose1)/1.5(-dose2)vs 1.5 NMB; 7.8% (RVX group) vs 5.3
Weitz, 2017 (EINSTEIN-CHOICE)[42]	3,365, age > 18 yr, acute DVT or PE	Dose 1; RVX (1007) Dose 2; RVX (1127)	Aspirin 100mg/day	1.5(dose1)/1.2(dose2) vs 4.4	MB; 0.1 (dose1)/0(-dose2) vs 0.1

APX; apixaban, DAB; dabigatran, EDX; edoxaban, RVX; rivaroxaban, CHF; congestive heart failure, ARDS; acute respiratory distress syndrome, IBD; inflammatory bowel disease, ENX; enoxaparin, bid; twice daily, d; day(s), S.C.; subcutaneously, OD; once daily, vs; versus, N/A; not mention, TIX; tinzaparin, FON; fondaparinux, n; number of study population, DVT; deep vein thrombosis, PE; pulmonary embolism, mo.; month(s), q; every, hr.; hour(s), NS; not statistically significant, MB; major bleeding, NMB; nonmajor bleeding

mg once daily had lower venous thrombosis related complications and major bleeding complications [41].

An EINSTEIN-CHOICE study compared rivaroxaban among therapeutic dose (20 mg/day), prophylactic dose (10 mg/day) and aspirin (control) in the extension phase; they found that prophylactic dose had a significantly reduced VTE related complications. The prophylactic dose group also had low major bleeding events when compared to therapeutic and control group [42]. In XALIA (postmarketing) cohort study, 3,449 VTE patients had been enrolled comparing rivaroxaban and standard treatment regimen. This study showed a statistically significant difference in VTE related complications (2.1 vs 3.0; $p < 0.001$), but no difference in safety outcomes between two groups ($p = 0.77$) [41].

5.11 Clinical practice of DOACs

Clinical applications of two DOACs (dabigatran and edoxaban) need to have heparin-bridging at the start [43]. Some antimalarial (quinidine), anti-fungal (ketoconazole), anti-tuberculosis (rifampicin) and antibiotic medications (clarithromycin) can increase DOACs-drug interactions via P-gp or CYP3A4 pathways [44]. Moreover, all DOAC doses need to be adjusted among renally impaired patients. The recommendation still suggests LMWH therapy for VTE patients with active malignancy because those patients attributed to small subgroups in DOACs studies [31-38,40-42,45,46].

6 Discussion

Thrombin inhibitor and FXa inhibitor are classified as new classes of anticoagulants. They have similar pharmacokinetic and pharmacodynamic properties. Their benefits are good oral absorption, short time to high peak concentration, less drug-drug or drug-food interactions and no need for blood monitoring. The data showed non-inferior for VTE treatment with DOACs compared with the conventional regimen (LMWH followed by VKA) in terms of VTE related complications and major bleeding.

In cases of travel-related thrombosis, DOACs is a great option for patients with poor compliance or high risk to drug-drug interactions. According to our reviewed data, all DOACs can be used to treat travel-related VTE as there is no evidence suggesting that it is different from VTE in general. The exception is VTE patients who also have active malignancy as LMWH for the first 3-6 months is the preferred treatment and data on DOACs are rather limited. In addition, there is a concern regarding the lack of antidotes for severe bleeding events or requirement for urgent invasive intervention in DOACs.

In patients, who have a history of previous unprovoked or travel-related VTE and have stopped anticoagulant treatment, are considered high risk for VTE under long haul flights. The studies on the extended therapy may be applied to these patients. Current data suggest that we may use prophylactic doses of DOACs which are much more convenient than LMWH injections. A dose of DOACs can cover for 24 hours.

On the other hand, data on primary prophylaxis using DOACs are limited as the conventional medication is still LMWH. The literature on DOACs is limited mainly to major orthopedic surgery which is only an approved indication

for DOACs. Therefore, patients who had recent major orthopedic surgery can use DOAC prophylaxis. A study using rivaroxaban in acute medically-ill patients showed a non-inferior efficacy of DOACs, but there is an increase in bleeding risk [47]. However, there is no reason for ineffectiveness of DOACs for VTE prophylaxis in other conditions, and a clinical trial on DOACs in this particular condition is unlikely. Because of its practicality, DOACs may be used off-label for VTE prevention of travel-related VTE. However, we need to have more clinical trial data among very high-risk patients (especially with active malignancy) before recommending DOACs.

7 Conclusion

Clinical data on VTE prophylaxis for travel-related VTE are still rather limited. Physicians must balance between risks of thrombosis and bleeding in an individual patient. Consideration on the patient's risk score and traveling schedule is helpful. Current clinical trial data suggest that DOACs can be used to treat travel-related VTE. Although the direct clinical data for primary prophylaxis is lacking, there is no rationale to suggest that DOACs are not effective in this indication.

Disclosures

This work was supported by Prasert Prasarttong—Osoth Research Foundation which is operated by the Medical Association of Thailand. All authors have no conflict of interest. Review concept, data collection, and data interpretation were contributed by Chamnanchanunt S. and Rojnuckarin P. The manuscript was written primarily by Chamnanchanunt S. The manuscript was revised by Chamnanchanunt S. and Rojnuckarin P.

References

- [1] Jacobson B.F., Munster M., Smith A., Burnand K.G., Carter A., Abdool-Carrim A.T., et al., The BEST study--a prospective study to compare business class versus economy class air travel as a cause of thrombosis, *S. Afr. Med. J.*, 2003, 93(7), 522-528
- [2] Martinelli I., Taioli E., Battaglioli T., Podda G.M., Passamonti S.M., Pedotti P., et al., Risk of venous thromboembolism after air travel: interaction with thrombophilia and oral contraceptives, *Arch. Intern. Med.*, 2003, 163(22), 2771-2774
- [3] Perez-Rodriguez E., Jimenez D., Diaz G., Perez-Walton I., Luque M., Guillen C., et al., Incidence of air travel-related pulmonary embolism at the Madrid-Barajas airport, *Arch. Intern. Med.*, 2003, 163(22), 2766-2770
- [4] Homans J., Thrombosis of the deep leg veins due to prolonged sitting, *N. Engl. J. Med.*, 1954, 250(4), 148-149
- [5] Ferrari E., Chevallier T., Chapelier A., Baudouy M., Travel as a risk factor for venous thromboembolic disease: a case-control study, *Chest*, 1999, 115(2), 440-444
- [6] Kraaijenhagen R.A., Haverkamp D., Koopman M.M., Prandoni P., Piovella F., Buller H.R., Travel and risk of venous thrombosis, *Lancet*, 2000, 356(9240), 1492-1493
- [7] Samama M.M., An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study, *Arch. Intern. Med.*, 2000, 160(22), 3415-3420
- [8] Scurr J.H., Machin S.J., Bailey-King S., Mackie I.J., McDonald S., Smith P.D., Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial, *Lancet*, 2001, 357(9267), 1485-1489
- [9] Belcaro G., Geroulakos G., Nicolaidis A.N., Myers K.A., Winford M., Venous thromboembolism from air travel: the LONFLIT study, *Angiology*, 2001, 52(6), 369-374
- [10] Belcaro G., Cesarone M.R., Shah S.S., Nicolaidis A.N., Geroulakos G., Ippolito E., et al., Prevention of edema, flight microangiopathy and venous thrombosis in long flights with elastic stockings. A randomized trial: The LONFLIT 4 Concorde Edema-SSL Study, *Angiology*, 2002, 53(6), 635-645
- [11] Belcaro G., Cesarone M.R., Nicolaidis A.N., Ricci A., Geroulakos G., Shah S.S., et al., Prevention of venous thrombosis with elastic stockings during long-haul flights: the LONFLIT 5 JAP study, *Clin. Appl. Thromb. Hemost.*, 2003, 9(3), 197-201
- [12] Cesarone M.R., Belcaro G., Nicolaidis A.N., Ricci A., Geroulakos G., Ippolito E., et al., Prevention of venous thrombosis in long-haul flights with Flite Tabs: the LONFLIT-FLITE randomized, controlled trial, *Angiology*, 2003, 54(5), 531-539
- [13] Hughes R.J., Hopkins R.J., Hill S., Weatherall M., Van de Water N., Nowitz M., et al., Frequency of venous thromboembolism in low to moderate risk long distance air travellers: the New Zealand Air Traveller's Thrombosis (NZATT) study, *Lancet*, 2003, 362(9401), 2039-2044
- [14] Schwarz T., Siebert G., Oettler W., Halbritter K., Beyer J., Frommhold R., et al., Venous thrombosis after long-haul flights, *Arch. Intern. Med.*, 2003, 163(22), 2759-2764
- [15] Wright H.P., Osborn S.B., Effect of posture on venous velocity, measured with ²⁴NaCl, *Br. Heart J.*, 1952, 14(3), 325-330
- [16] Bendz B., Rostrup M., Sevre K., Andersen T.O., Sandset P.M., Association between acute hypobaric hypoxia and activation of coagulation in human beings, *Lancet*, 2000, 356(9242), 1657-1658
- [17] Luvira V., Chamnanchanunt S., Thanachartwet V., Phumratanapapin W., Viriyavejakul A., Cerebral venous sinus thrombosis in severe malaria, *Southeast Asian J. Trop. Med. Public Health*, 2009, 40(5), 893-897
- [18] Bagshaw M., Jet leg pulmonary embolism, and hypoxia, *Lancet*, 1996, 348(9024), 415-456
- [19] Zotz R.B., Kauschat-Bruning D., Bramlage P., Thromboembolic risk and prophylaxis in hospitalized surgical and internal medicine patients. German results of the international

- ENDORSE study, *Dtsch. Med. Wochenschr.*, 2009, 134(43), 2163-2169
- [20] Watson H.G., Baglin T.P., Guidelines on travel-related venous thrombosis, *Br. J. Haematol.*, 2011, 152(1), 31-34
- [21] Kearon C., Akl E.A., Comerota A.J., Prandoni P., Bounameaux H., Goldhaber S.Z., et al., Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, *Chest*, 2012, 141(2), e419S-94S
- [22] Schobersberger W., Toff W.D., Eklof B., Fraedrich G., Gunga H.C., Haas S., et al., Traveller's thrombosis: international consensus statement, *Vasa*, 2008, 37(4), 311-317
- [23] Kahn S.R., Lim W., Dunn A.S., Cushman M., Dentali F., Akl E.A., et al., Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, *Chest*, 2012, 141(2), e195S-226S
- [24] Kuipers S., Cannegieter S.C., Middeldorp S., Rosendaal F.R., Buller H.R., Use of preventive measures for air travel-related venous thrombosis in professionals who attend medical conferences, *J. Thromb. Haemost.*, 2006, 4(11), 2373-2376
- [25] Hagan M.J., Lambert S.M., A randomised crossover study of low-ankle-pressure graduated-compression tights in reducing flight-induced ankle oedema, *Med. J. Aust.*, 2008, 188(2), 81-84
- [26] Loew D., Gerlach H.E., Altenkämper K.H., Schneider B., Effect of Long-Distance Flights on Oedema of the Lower Extremities, *Phlebology*, 1998, 13(2), 64-67
- [27] Kuipers S., Schreijer A.J., Cannegieter S.C., Buller H.R., Rosendaal F.R., Middeldorp S., Travel and venous thrombosis: a systematic review, *J. Intern. Med.*, 2007, 262(6), 615-634
- [28] Kearon C., Gent M., Hirsh J., Weitz J., Kovacs M.J., Anderson D.R., et al., A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism, *N. Engl. J. Med.*, 1999, 340(12), 901-907
- [29] Franco L., Giustozzi M., Agnelli G., Becattini C., Anticoagulation in patients with isolated distal deep vein thrombosis: a meta-analysis, *J. Thromb. Haemost.*, 2017, (15), 13-11
- [30] Ringwald J., Grauer M., Eckstein R., Jelinek T., The place of new oral anticoagulants in travel medicine, *Travel Med. Infect. Dis.*, 2014, 12(1), 7-19
- [31] Schulman S., Kearon C., Kakkar A.K., Mismetti P., Schellong S., Eriksson H., et al., Dabigatran versus warfarin in the treatment of acute venous thromboembolism, *N. Engl. J. Med.*, 2009, 361(24), 2342-2352
- [32] Schulman S., Kearon C., Kakkar A.K., Schellong S., Eriksson H., Baanstra D., et al., Extended use of dabigatran, warfarin, or placebo in venous thromboembolism, *N. Engl. J. Med.*, 2013, 368(8), 709-718
- [33] Schulman S., Kakkar A.K., Goldhaber S.Z., Schellong S., Eriksson H., Mismetti P., et al., Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis, *Circulation*, 2014, 129(7), 764-772
- [34] Botticelli Investigators W.C., Buller H., Deitchman D., Prins M., Segers A., Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study, *J. Thromb. Haemost.*, 2008, 6(8), 1313-1318
- [35] Agnelli G., Buller H.R., Cohen A., Curto M., Gallus A.S., Johnson M., et al., Oral apixaban for the treatment of acute venous thromboembolism, *N. Engl. J. Med.*, 2013, 369(9), 799-808
- [36] Agnelli G., Buller H.R., Cohen A., Curto M., Gallus A.S., Johnson M., et al., Apixaban for extended treatment of venous thromboembolism, *N. Engl. J. Med.*, 2013, 368(8), 699-708
- [37] Hokusai V.T.E.I., Buller H.R., Decousus H., Grosso M.A., Mercuri M., Middeldorp S., et al., Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism, *N. Engl. J. Med.*, 2013, 369(15), 1406-1415
- [38] Einstein Investigators, Bauersachs R., Berkowitz S.D., Brenner B., Buller H.R., Decousus H., et al., Oral rivaroxaban for symptomatic venous thromboembolism, *N. Engl. J. Med.*, 2010, 363(26), 2499-2510
- [39] Prins M.H., Lensing A.W., Bauersachs R., van Bellen B., Bounameaux H., Brighton T.A., et al., Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies, *Thromb. J.*, 2013, 11(1), 21
- [40] Ageno W., Mantovani L.G., Haas S., Kreutz R., Haupt V., Schneider J., et al., XALIA: rationale and design of a non-interventional study of rivaroxaban compared with standard therapy for initial and long-term anticoagulation in deep vein thrombosis, *Thromb. J.*, 2014, 12, 16
- [41] Yamada N., Hirayama A., Maeda H., Sakagami S., Shikata H., Prins M.H., et al., Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism - the J-EINSTEIN DVT and PE program, *Thromb. J.*, 2015, 13, 2
- [42] Weitz J.J., Lensing A.W.A., Prins M.H., Bauersachs R., Beyer-Westendorf J., Bounameaux H., et al., Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism, *N. Engl. J. Med.*, 2017, 376(13), 1211-1222
- [43] Lippi G., Favaloro E.J., Mattiuzzi C., Combined administration of antibiotics and direct oral anticoagulants: a renewed indication for laboratory monitoring?, *Semin. Thromb. Hemost.*, 2014, 40(7), 756-765
- [44] Lippi G., Favaloro E.J., Franchini M., Dangers in the practice of defensive medicine in hemostasis testing for investigation of bleeding or thrombosis: part I-routine coagulation testing, *Semin. Thromb. Hemost.*, 2014, 40(7), 812-824
- [45] Wang Y., Wang C., Chen Z., Zhang J., Liu Z., Jin B., et al., Rivaroxaban for the treatment of symptomatic deep-vein thrombosis and pulmonary embolism in Chinese patients: a subgroup analysis of the EINSTEIN DVT and PE studies, *Thromb. J.*, 2013, 11(1), 25
- [46] Farge D., Bounameaux H., Brenner B., Cajfinger F., Debourdeau P., Khorana A.A., et al., International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer, *Lancet Oncol.*, 2016, 17(10), e452-e66
- [47] Cohen A.T., Spiro T.E., Buller H.R., Haskell L., Hu D., Hull R., et al., Rivaroxaban for thromboprophylaxis in acutely ill medical patients, *N. Engl. J. Med.*, 2013, 368(6), 513-523